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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,908	09/15/2003	Martin Vaupel	CS-7907LeA 36,217	1270

34469 7590 03/23/2006

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EXAMINER	
BULL, CHRISTOPHER	

ART UNIT	PAPER NUMBER
1655	

DATE MAILED: 03/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,908	VAUPEL ET AL.	
	Examiner	Art Unit	
	Christopher Bull	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *6-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 Sept 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20 Apr, 7 Jun 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The abbreviation FPPase will be used for farnesyl-pyrophosphate synthase throughout this action.

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-5, in the reply filed on 6 Feb 2006 is acknowledged.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 6-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6 Feb 2006.

Claims 1-5 are presented for consideration on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as being unclear as to what constitutes a farnesyl-pyrophosphate synthase inhibition assay. There are no steps recited and no criteria for what constitutes inhibition.

Claim 2 in part a) recites using a host cell which expresses "a sufficient amount" of an FPPase, without explaining how to recognize what constitutes an insufficient amount, i.e., it is unclear what problem(s) are avoided by using a sufficient amount.

Claim 2 also is unclear in part a) with respect to intention and/or grammar. Paraphrasing part a) for the structure, it is unclear which is Applicant's intent:
a [host cell with {FPPase or a polypeptide having FPPase activity}], as opposed to:
a [host cell with FPPase] or a {polypeptide with FPPase activity}.

Claims 3-5 depend from Claims 1 and 2 but do not resolve the issues with Claims 1 and 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. (US 2002/0035058 published 21 Mar 2002, parent filed 12 May 1997).

Brown et al. teach using human cells to assay for inhibition of FPPase. (paragraphs 172-179 and 182). Their claim 33 recites (please note that they use isopentenyl pyrophosphate isomerase = IPI; and prenyl transferase = FPPase):

"A method for evaluating the therapeutic activity of a putative drug (e.g. a bisphosphonate) comprising the steps of:

(a) contacting the drug with the IPI and/or prenyl transferase as defined in any one of claims 24-31, and either

(b) measuring the binding affinity of the putative drug for the IPI and/or prenyl transferase, or

(c) measuring the extent of inhibition imposed by the putative drug on IPI and/or prenyl transferase activity."

This claim of Brown et al. reads directly on Claims 1 and 2.

Accordingly, Brown et al. is deemed to anticipate Claims 1-2.

Claims 1 is rejected under 35 U.S.C. 102(b) as being anticipated by McClard et al. (1987 JACS 109, 5544-5545).

McClard et al. teach using avian liver farnesyl-diphosphate synthase to assay for inhibition by substrate analogs wherein the pyrophosphate group is replaced with a

corresponding methanediphosphonate group (page 5544). These proved to be competitive inhibitors, as well as slow substrates of avian liver FPPase (end of 5544 and beginning of 5545). FPPase is an enzyme essential in all eukaryotes to the proper functioning of membranes (see Brown et al. above, paragraph 185). There is substantial identity in biosynthetic pathway and even in sequence homology between the enzymes of fungi and the higher animals. Therefore, inhibitors of avian FPPase will be inhibitors of fungal FPPase. McClard et al. recognized that cumulative inhibition of succeeding steps in the pathway could occur (end of the penultimate paragraph, page 5545): "The accumulation of nonhydrolyzable allylic analogues should be particularly devastating to higher polyprenyl diphosphate synthetases which catalyze multiple 1'-4-condensations." The clear expectation is that inhibitors of FPPase will prove biocidal.

Claim 1 is drawn to a method of identifying fungicides, comprising assaying a chemical compound in a farnesyl-pyrophosphate synthase inhibition assay. There being no limitations recited in the claim as to organism in the FPPase inhibition assay and no requirement to show fungicidal activity other than by inhibition in an FPPase assay, any inhibition in any FPPase assay from whatever source by whatever method will read on this claim. As summarized above, McCord et al. demonstrate compounds showing inhibition in an FPPase assay.

Accordingly, McClard et al. is deemed to anticipate Claim 1.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergstrom et al. (1 Jan 2000 ABB 373, 231-241).

Bergstrom et al. teach using human or rat liver farnesyl-diphosphate synthase to assay for inhibition by alendronate, which proved a potent inhibitor (pages 237-238 Table I). Assay was by HPLC after acid hydrolysis (page 233 upper left). Bergstrom et al. then demonstrate that this inhibition could be observed in osteoblasts under cell culture conditions (page 239). Activity was assayed using ^{14}C labeled mevalonate and determining products by TLC after acid hydrolysis of the phosphate (page 234).

Claim 1 is drawn to a method of identifying fungicides, comprising assaying a chemical compound in a farnesyl-pyrophosphate synthase assay. There being no limitations recited in the claim, any inhibition in any FPPase assay from whatever source by whatever method will read on this claim. The teachings of Bergstrom et al. will be compared to Claim 2 (and thereby to Claim 1 - assaying in FPPase assay):

a) contacting a host cell with substrates and test compound;
[osteoclasts (animal cells that remodel bones) contacted with inhibitors page 238]

b) comparing the FPPase activity with or without test compound; and
[ALN inhibits labeling of nonsaponifiable lipids (sterols), products after FPPase p 238]

c) identifying the test compound.
Bergstrom et al. proved ALN was an FPPase inhibitor in these cells, and that the nitrogen containing bisphosphonates were distinct in FPPase inhibition from other bisphosphonates. In so doing, Bergstrom et al. identified the chemical compound that specifically inhibits FPPase.

Accordingly, Bergstrom et al. is deemed to anticipate Claims 1 and 2, since proving fungicidal activity is not a requirement of either claim.

Claims 1 and 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Turek et al. (14 Apr 2001 J Org Chem 66, 3253-3264).

Turek et al. mainly teach photoaffinity labels for a subsequent enzyme,(i.e., after FPPase in the pathways), based on structures that resemble the productsw of the FPPase reactions (page 3255). However, they tried them as inhibitors of FPPase as well (page 3261 lower left and upper right).These compounds bound to FPPase competitively with the FPPase product, farnesyl-pyrophosphate, since that compound greatly diminished photoaffinity labeling by their two inhibitors (page 3261). Turek et al. used ^{32}P labeled photolabels, and observed phosphorimaging to detect labeled protein.

Claim 1 is drawn to a method of identifying fungicides, comprising assaying a chemical compound in a farnesyl-pyrophosphate synthase assay. There being no limitations recited in the claim, any inhibition in any FPPase assay from whatever source by whatever method will read on this claim. Accordingly, a demonstration of inhibition in direct binding to an FPPase polypeptide as done by Turek et al. reads on assaying a chemical compound in a farnesyl-pyrophosphate synthase inhibition assay.

Claim 3 recites the additional limitation of using a fungal FPPase. Turek et al. use a yeast FFPase (page 3261). Applicants use a yeast FPPase, and essentially state that yeast are a form of fungi (page 10 lines 19-26). Accordingly, Turek et al. is deemed to anticipate Claim 3.

Claim 4 recites "wherein the inhibition of the enzyme activity of the FPPase is measured on the basis of the amount of phosphate group, determined with a phosphate detection reagent. Turek et al. affixed the photoaffinity product label to the FPPase,

jamming the active site. Amount bound, and hence % inhibition, was measured on the basis of the amount of ^{32}P in a phosphate group, and that the amount was determined with a phosphate detection reagent in the form of a scintillation element in the phosphorimager. Accordingly, Turek et al. is deemed to anticipate Claim 4.

Claims 1-2 are rejected under 35 U.S.C. 102(e) as being anticipated by Bergstrom et al. (US 2004/0235797 published 25 Nov. 2004, parent filed 25 Feb. 2000).

Bergstrom et al. teach methods of identifying compounds useful as inhibitors of FPPase (Abstract). Bergstrom et al. in their claim 1 recite:

"1. A method for identifying an inhibitor of farnesyl diphosphate synthase comprising:

a).contacting a putative farnesyl diphosphate synthase inhibitor with a farnesyl diphosphate synthase solution, and

b). determining the farnesyl diphosphate synthase activity of said solution with a farnesyl diphosphate synthase solution not contacted with said putative inhibitor."

This claim and Examples 4-6 of Bergstrom et al. read directly on Claims 1 and 2.

Accordingly, Bergstrom et al. is deemed to anticipate Claims 1-2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. (US 2002/0035058 published 21 Mar 2002, parent filed 12 May 1997) in view of Atabekov et al. (US 4,808,522 issued 28 Feb 1989).

Brown et al. teach using human cells to assay for inhibition of FPPase. (paragraphs 172-179 and 182). Their claim 33 recites (please note that they use isopentenyl pyrophosphate isomerase = IPI; and prenyl transferase = FPPase):

"A method for evaluating the therapeutic activity of a putative drug (e.g. a bisphosphonate) comprising the steps of:

(a) contacting the drug with the IPI and/or prenyl transferase as defined in any one of claims 24-31, and either

(b) measuring the binding affinity of the putative drug for the IPI and/or prenyl transferase, or

(c) measuring the extent of inhibition imposed by the putative drug on IPI and/or prenyl transferase activity."

Claim 14 of Brown et al. further recites "Use of an inhibitor of IPI and/or prenyl transferase as an herbicide or fungicide."

Brown et al. do not teach an FPPase assay wherein inhibition is measured on the basis of a phosphate detection reagent. The product of FPPase is pyrophosphate.

Atabekov et al. teaches using Malachite Green and ammonium molybdate in acid to measure phosphate within the context of ELISA assays using pyrophosphatases as the indicator enzyme (Col 4). Atabekov et al. beneficially teaches that acid will cleave the pyrophosphate to phosphate for the assay (Col 3), and that very sensitive assays can be made using this reagent (Example 8, Table 5).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ a pyrophosphate assay with an FPPase enzyme that releases pyrophosphate as a product via the instantly claimed steps, because Brown et al. teach that it is within the ordinary skill in the art to identify inhibitors of FPPase and Atabekov et al. teaches that it is within the ordinary skill in the art to use a colorimetric phosphate assay in a high throughput screening format. This combination reads on Claims 1-2 and 4.

One would have been motivated to do so for the expected benefit of eliminating the use of radioactive substrates and products, and the benefit of a high throughput format, as taught by Atabekov et al.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown et al. in view of Atabekov et al., and further in view of Grove et al. (2000 J Bone and Mineral Research 15, 971-981).

The teachings of Brown et al. and Atabekov et al. in combination have been discussed above and are applied as before.

They beneficially note literature studies on (paragraph 121-123) slime mold FPPase sources, and expect bisphosphonate inhibitors to be fungicidal (paragraph 97) when tested against slime mold cells. Claim 14 of Brown et al. further recites "Use of an inhibitor of IPI and/or prenyl transferase as an herbicide or fungicide."

Brown et al. do not teach an FPPase assay wherein inhibition is measured a fungal FPPase, or contacting a candidate inhibitor to a fungus.

Grove et al. teach testing aminobisphosphonate drugs on the slime mold, *Dictyostelium discoideum* (Table 2 page 977), both as inhibitors of FPPase and as fungal growth inhibitors.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to employ the fungal FPPase enzyme assays and the growth inhibition methods with the method to identify compounds that inhibit FPPase activity measured by phosphate release via the instantly claimed steps, because Grove et al. teach that it is within the ordinary skill in the art to identify inhibitors of fungal FPPase and screen them as fungicides while the combination of Brown et al. and Atabekov et al. teaches that it is within the ordinary skill in the art to identify inhibitors of

FPPase based on a colorimetric phosphate assay in a high throughput screening format as possible fungicides. This combination reads on Claims 3 as specifically inhibiting a fungal FPPase (page 977 left) and on Claim 5 as directly measuring inhibition of fungal growth (pages 977-978).

One would have been motivated to do so for the expected benefit of eliminating earlier any falsely positive fungicidal candidates identified in the high throughput screening format for candidate fungicides, as taught by the combination of Brown et al. and Atabekov et al.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Bull whose telephone number is (571) 272-1327. The examiner can normally be reached on 7:30-4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1655

cb

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